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Heparin-free hemodialysis

Hemodializa bez heparyny

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Summary

Hemodialysis is the most widely applied renal replacement therapy. Due to the fact that the hemocyte - dialyzer contact leads to the activation of the coagulation pathway, adequate anticoagulation to provide fluent blood flow is crucial. Since the standard parenteral use of heparin is not free from complications and may increase already raised bleeding risk in renal patients, the alternative methods of performing hemodialysis, including heparin-free procedures, are being investigated. These include the usage of anticoagulants regionally in the extracorporeal circuit or repeated saline flushes or other substituting compounds. Citrate module has already become the standard anticoagulant in intensive care for patients on continuous hemofiltration. Its usage in intermittent dialysis program requires some protocol modifications, but it is a valuable input in the development of heparin-free strategies. The other approach that allows reduced heparin usage is the use of an airless dialysis tubing system. Amongst coated dialyzer membranes, the one with heparinized hydrogel polyacrylonitrile was perceived as a significant step forward. Despite the fact that innovative strategies may turn out to be time and resource consuming and not always free of side-effects, they are worth investigating.

Keywords: **hemodialysis • heparine • anticoagulation • dialyzer • clotting • bleeding**

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Abbreviations: **ACT** – activated clotting time, **AKI** – acute kidney injury, **aPTT** – activated partial thromboplastin time, **CRRT** – continuous renal replacement therapy, **ESRD** – end-stage renal disease, **HA** – heparin-albumin solution, **HD** – hemodialysis, **HIT** – heparine induced thrombocytopenia, **iCa** – ionized calcium, **KDIGO** – Kidney Disease: Improving Global Outcomes, **LMWH** – low molecular weight heparin, **PES** – polyethersulfone, **URR** – urea-reduction ratio, **VP** – venous pressure.

INTRODUCTION

Blood cells coming into contact with the tubing system and dialysis membrane of the dialyzer triggers cell activation via complement pathway, bradykinine and kallikrein activation and finally leads to the release of histamine, leukotriens, prostaglandines, IL-1 and TNF-alpha. Currently used hollow fiber synthetic dialyzers are characterized by a minor inflammatory response and lower oxidative stress but yet evoke coagulation cascade. Therefore, hemodialysis requires effective anticoagulation in order to avoid extracorporeal blood circuit clotting.

Although standard systemic heparinization is relatively safe and effective, its long-term use is associated with complications including platelet dysfunction, thrombocytopenia, osteoporosis, allergic reactions and increase of bleeding risk. Apart from anticoagulant-related risk of bleeding, one should remember that end-stage renal disease patients are already at an increased risk of hemorrhage due to higher incidence of gastrointestinal events (erosions, surface inflammations, vascular malformations), azotemia-associated platelet dysfunctions and altered platelet vessel wall interactions.

Systemic heparinization for hemodialysis (HD) has been associated with bleeding complications in up to 26% of treatments in past decades [44]. Heparin-induced thrombocytopenia (HIT) with immune mediated mechanism is another cause for heparin-free dialysis. One should remember that a patient with HIT is actually prothrombotic and another systemic anticoagulant is required.

Hemorrhagic complications related to anticoagulation encouraged the development of numerous strategies increasing patient safety from tight, precisely controlled heparinization to anticoagulant-free hemodialysis.

Proposed alternatives to systemic heparin anticoagulation were as follows, chronologically: regional heparinization of the extracorporeal circuit [17], precisely controlled low-dose heparinization [5] and repeated saline flushes [25]. There have been other agents proposed instead of heparin: citrate [22], prostacyclin [36, 45], gabexate mesilate [37], nafamostat mesilate [1], recombinant hirudin [40] and fondaparinux [11, 18]. Prostacyclin, antiplatelet agent with a short half-life, has been proven as an effective anticoagulant in HD but wide application is limited by its side effects, such as hypotension, flushing, gastrointestinal complaints and, finally, high costs [36]. Nafamostat is a serine protease inhibitor with a very short half-life (up 10 min.) and acts by suppressing neutrophil's activity. Its use only in regional anticoagulation is limited mainly by costs and a low number of studies in HD patients. Recombinant hirudin, a thrombin-specific inhibitor, due to accumulation in ESRD [40, 41], is not safer than heparin (anticoagulation effect persist 8 hours after HD despite aPTT normalization) and may be reversed only with activated prothrombin complex concentrate.

Technological modifications in tubing systems and dialyzers are other promising approaches.

This mini review encompasses the most practical and promising strategies of conducting heparin free-dialysis.

HEPARIN-AVOIDANCE HD PROTOCOLS

Studies have shown that heparin-free (anticoagulant free) hemodialysis is a possible and safe solution in patients with active bleeding [8, 31]. In the prospective analysis of 101 heparin-free hemodialyses, published in 1983, extracorporeal clotting occurred in fewer than 2% of procedures [3].

It was suggested that heparin-free hemodialysis might result in increased fibrin–fibrinogen deposition in the dialyzer with a subsequent reduction of its efficacy. Multiple HD procedures without any anticoagulation may lead to consumption coagulopathy [20, 34], but with the use of the synthetic, more biocompatible (e.g. polysulphone) membranes this complication is rare. Romao et al. checked the conventional hemostasis parameters in 10 HD patients in 2 consecutive sessions during (every 30 min.) and after HD, i.e. fibrinogen, prothrombin time, platelet count, antithrombin III, and fibrin–fibrinogen degradation products [23]. All coagulation parameters remained at normal levels during hemodialysis without anticoagulation and did not differ from those during a conventional procedure. Hemodialysis without anticoagulation in this study was associated with greater decline in circulating fibrinogen and fibrin deposition on the dialyzer membranes, and more importantly, without any change in dialyzer efficiency.

One strategy to achieve anticoagulant-free HD is saline flushing of the dialysis circuit. This technique was described in 1979, and various protocols have been published since then. In general, it involves saline infusions in 100-200 ml boluses every 15-60 minutes. With this approach, clotting requiring dialyzer change ranges from 3% to 10% of sessions.

The most commonly used protocols of heparin-free hemodialyses is based on regular saline flushes (table 1) or pre-dilution mode and high flow rate.

Pre-dilution mode is safe in most patient group and is practiced in intensive care units. Since hemodiafiltration is also available in ambulatory dialysis (on-line HDF), this method is worth consideration. It is associated with reduced clearance of small solute though.

High blood flow rate (>300-350 ml/min) relies on a good vessel (size) and position of the needle/catheter tip. Another important requirement is for the patient to be calm and hemodynamically stable.

The choice of the method depends on the standard of care in the center. One example of a protocol with proven effect is displayed in Table 2.

A frequent practice, also in authors' facility, is the minimum-dose heparin regimen for anticoagulation during hemodialysis in patients at risk of bleeding. Heparin is given as a bolus at the start of the dialysis treatment, with a mid-treatment dose to maintain suitable anticoagulation. The protocol usually involves boluses of 300-500 units of heparin every 30 minutes to keep the activated partial thromboplastin time (aPTT) 1.5-2 times above upper lab limit or activated clotting time (ACT) in the range of 150-200 seconds. Alternately, a continuous infusion of heparin with frequent aPTT/ACT monitoring can be used to achieve the same degree of anticoagulation. The advantage of this approach is that no additional equipment is need. The disadvantage is that a minimal degree of anticoagulation of the patient still occurs.

REGIONAL CITRATE ANTICOAGULATION

Citrate acts as an anticoagulant by chelating ionized calcium (iCa), a necessary cofactor for clotting. An iCa concentration below 0.25 mmol/L guarantees maximal anticoagulation. By chelating calcium and magnesium, citrate may reduce complement activation induced by blood contact with the membrane of the dialyzer, thus improving the biocompatibility of the dialysis circuit. Unlike heparin, citrate has no antigenicity. Citrate is easily dialyzable (molecular weight of trisodium citrate is 294 Da), with more than 80 % removal through the high-flux membrane. The remains of citrate enter the circulation where it is quickly metabolized in the liver, muscles and kidneys.

Citrate has already become the standard anticoagulant (as recommended by KDIGO) in acute kidney injury, requiring continuous renal replacement therapy (CRRT), both for adults and children, with the citrate module being a part of modern CRRT apparatus [14].

Table 1. Various Heparin-free Saline Flush Protocols

Design, population	UF (liters per session or per hour) (mean ± SD)	Circuit clotting (%)	Saline flushes	Ref.; Number of patients
Retrospective Inpatient, ESRD and AKI	1 ± 0.817 L / session in treatments that clotted vs 2 ± 1.366 in those that did not	1	100 mL q15 min	Sahota (n=400) [28]
Retrospective Inpatient, ESRD and AKI	0.891 ± 0.971 L / session	5	50 mL q60 min	Stamatiadis [35] (n=1,224)
Retrospective Inpatient, in kidney transplant recipients (perioperative and postoperative), ESRD and AKI	No data	5 totally 6 partially	100 mL q30 min	Sanders (n=158) [29]
Prospective Inpatient, mostly posttransplant AKI, but some ESRD	No data	10	250-300 mL q15 min	Casati [3] (n=101)
Prospective Inpatient, mostly ICU, strictly AKI	1.36 ± 0.003 liters per hour	2	50-100 mL q15 min	Schwab [31] (n=262)

Abbreviation: AK - acute kidney injury; ESRD - end-stage renal disease; ICU - intensive care unit.

Table 2. The protocol of heparin-free dialysis based on regular saline flushes

- Priming the dialyzer with saline at a pump speed (PS) of 200 mL/min.
- Recirculating the saline at PS 500 mL/min for 30 s or until all air has been removed from the bloodlines and dialyzer.
- Continued recirculation of the saline at PS 200 mL/min for 10 min.
- During the HD treatment, the dialyzer is flushed every 15 min with 100 mL of saline. This is achieved by clamping off the bloodline and opening up a preattached bag of saline to the blood pump until 100 mL had been flushed through the dialyzer. This is done using the same pump rate that is used for the blood during treatment, and thus the saline flush takes 15-20 s. The total volume amount of saline flushes anticipated during a treatment is calculated into the total ultrafiltration fluid removed during the HD treatment.
- Unless contraindicated, blood flows of 300-350 mL/min are advisable

Regional citrate anticoagulation requires a calcium-free dialysate and two precise infusion pumps to maintain the dialyzer efficiency (figure 1). In the past, several groups have reported that calcium and citrate administration may cause hypernatremia, volume overload, acid–base disorders and hypo- or hypercalcemia [13, 42]. Although the citrate module is not yet available for intermittent hemodialysis, some centers elaborated own practical protocols (e.g. Ljubljana or Maribor, Slovenia). The dose of citrate is calculated as the percentage of blood flow and adjusted according to the post-dialyzer (or pre-dialyzer) ionized calcium level, targeted to 0.3-0.4 mmol/L. Before the hypocalcemic blood is returned to the patient, it must be supplemented with calcium. Maintaining normal ionized calcium in the patient's blood is the most important safety issue. The other key safety issues necessary to avoid the aforementioned side effects encompass the use of precise infusion pumps, point-of-care ionometers, high flux dialyzers (high citrate clearance) and adjustment of sodium and bicarbonate offered by modern hemodialysis monitors [9].

The use of calcium-containing dialysate during regional anticoagulation could have the advantage of simplifying the procedure and improving safety. Increased clotting in the dialysis circuit is a real drawback, though.

One of the advantages of citrate over anticoagulation, which encourages its use in chronic HD patients, is the reduction of hemodialysis-induced inflammatory response [2]. This strategy of heparin-free dialysis is promising especially for hospital-based centers, as the required equipment is already available on site.

HEPARIN ALBUMIN PRIMING

This concept is to use a heparin-albumin (HA) solution to rinse the dialysis circuit before start. In proposed protocol saline contained albumin (1 g/l) and heparin (5000 Units/L) is primed. Excess priming solution is removed by filling the circuit with blood at the starting point of treatment. In a retrospective study by Fransson et al. heparin-albumin priming resulted in reduced total dose of heparin per session on average (2000 *vs* 5500 IU in HA priming vs regular HD session, respectively). In the mentioned study additional heparin was given only upon suspicion of progressive clotting, assesed on the basis of observation of tubing system and dialyzer [7]. In this series no increased clotting in circuit/dialyzer and no incidence of bleeding was reported.

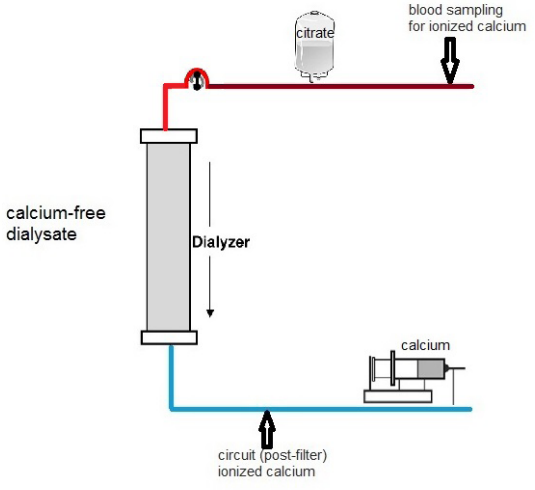

Fig. 1. Regional citrate anticoagulation during hemodialysis session

The same group published recently retrospective data derived from 1408 acute dialysis treatment protocols that included 321 patients [32]. After comparison of vulnerable patients (at risk of bleeding) receiving HA mixture priming with regular patients (no bleeding risk) the results showed that dialysis time was a little bit shorter (190 *vs* 197 minutes), and total dose of heparin was at median 1200 vs 5000 Units. The authors concluded that HA priming minimized the risk of clotting and enabled completipon of acute HD in vulnerable patients without increased bleeding, thus allowing completion of HD to the same extent as for standard HD.

REDUCTION OF BLOOD-AIR CONTACT IN TUBING SYSTEM

Recent progress in dialysis technology allows the use of airless dialysis tubing that minimizes blood-air interaction. The Streamline™ bloodlines (NxStage Medical, USA), which are designed to eliminate blood-air contact, serve as an example. This system measures arterial and venous pressure without blood-air contact, and a venous chamber runs without an air gap. The tubing enables blood flow to run in a non-turbulent manner with lower exposure to plastic tubes than the conventional system. A few small studies suggest that airless bloodlines improve dialysis efficiency and blood flow rates while reducing heparin usage [10, 33].

Recent reports on the use of heparin-free protocols with the utilization of airless tubes system show the possibility of inpatient hemodialysis in adults across all the access types with no circuit clotting. Sahota et al. used a protocol similar to the one displayed in Table 2 and reported that only 4 of 400 (1%) of the procedures clotted the dialysis circuit [28]. Such an extremely low clotting rate was not confirmed in other reports. Recently, Safadi et al. analyzed retrospectively 1200 HD sessions in 338 patients (204 ESRD, 134 AKI) using heparin avoidance protocol with the use of airless tubing set [27]. The median session lasted 211 minutes, heparin was prescribed in only 4.5% of sessions and circuit clotting rate was 5.2%. The effectiveness of airless tubes system seems lower than in the previous report, but the difference can be explained by clinical characteristics of the patients. In this retrospective study the most frequently used angioaccess was tunneled catheter (54%) and blood transfusions were performed during 4.5% HD sessions –

both are strong known risk factors of circuit clotting. Prophylactic heparin (to avoid deep vein thrombosis) was given to 45% of patients and another 35% received therapeutic systemic anticoagulation (warfarin or heparin). It seems that the use of airless dialysis tubing as a single maneuver to avoid anticoagulation for HD is not enough but in combination with other approaches, like heparin sparing protocol, it might be effective.

GENIUS SYSTEM

The Genius® system is based on the single-pass batch principle and consists of a 75 l glass tank completely filled with dialysate. During the treatment, fresh dialysate is taken from the top of the tank and is returned to the bottom after passing the dialyzer (fresh and used dialysate do not mix). The extracorporeal circuit does not contain drip chambers and thus isdevoid of contact between blood and air.

Citrate (regional) anticoagulation can be safely and effectively performed during intermittent Genius dialysis. Morgera et al. adjusted the citrate dose according to the post-filter iCa concentration (targeted values 0.5-0.7 mmol/l) [19]. Interestingly, calcium supplementation was not routinely required, which means that only one pump is needed. Schneider and coworkers showed that slow extended Genius hemodialysis with regional citrate anticoagulation is well tolerated and offers a safe and effective alternative to systemic anticoagulation in critically ill patients with AKI [30]. Another anticoagulant sparing approach already tested in the Genius system was covalent circuit coating with low molecular weight heparin (LMWH) for intermittent haemodialysis. LMWH surface coating (AOThel® coating) reduced thrombogenicity in vitro without releasing significant amounts of heparin from the surface [6].

COATED DIALYZER MEMBRANES

The introduction of membrane dialyzers with hydrogel polyacrylonitrile that was heparinized during the manufacturing process (Evodial™) heralded a breakthrough in the field of anticoagulant-free dialysis. Single reports suggested their usefulness in patients with active bleeding, giving the possibility of individualizing anticoagulation therapy by reducing the dose of heparin [15].

The HepZero study was a designed to compare heparin-free HD strategy with a heparin-grafted dialyzer. This was a randomized, multicenter international controlled trial [16]. Two hundred fifty one total maintenance HD patients at increased risk of hemorrhage were allocated to regular saline flushes/pre-dilution (depending on center standard) or a heparin coated dialyzer. The current standard-of-care resulted in high failure rates (50%). The success rate in the heparin-grafted membrane arm was significantly higher than in the control group (68.5% versus 50.4%), which was consistent for both standard-of-care modalities. The absolute difference between the heparin-grafted membrane and the controls was 18.2%. Unfortunately, the hypothesis of superiority of heparin-coated dialyzer at the +15% level was not reached. Clotting still occurred in 33% of the treatments with Evodial dialyzer.

Other beneficial features of heparin-grafted dialyzers apart from a heparin-sparing effect were reported. For instance: in a small clinical study by Rydzewska-Rosolowska et al., the use of Evodial for HD resulted also in cytokine reduction in the intradialytic period when compared to enoxaparine (fractionated heparin). They have found significant differences in the concentrations of chemoattractant protein 1 (MCP-1), endostatin and activin A, favoring Evodial dialyzer. The authors concluded that heparin-free dialysis with Evodial membrane might reduce proinflammatory cytokine concentration and, therefore, contribute to the improvement in endothelial function [26].

More than fifty studies have been published since vitamin E-coated membranes were proposed. The following effects were confirmed in relation to the aforementioned membranes: the improvement in the erythropoietin resistance index (no impact on other anemia parameters), a decrease in interleukin-6 levels and a significant increase in blood and erythrocytes vitamin E level [4]. Also, its anticoagulation properties were suggested, but no hard data is available.

The success rate of 4-hour heparin-free hemodialysis sessions applying vitamin E-coated and heparin-coated dialyzers was lower in a recent study by Islam et al. than previously reported in uncontrolled studies [12]. Vitamin E-coated and heparin-coated dialyzers exposed patients to similar and unacceptably high failure risk. A possible explanation of this can be found in Tsukao et al.'s study [39]. They stated that contact with vitamin E-coated surface reduces platelet activation mediated by the superoxide anions, probably by reducing the anions, but during the process of reduction the vitamin E-coated surface becomes oxidized itself, which again causes platelet activation. The beneficial effects of vitamin E-coated dialyzer in respect to platelet activation were counteracted by the formation of oxidized vitamin E.

Recently, preliminary results of TRIATHRON1 study testing hydrophilic dialysis membrane have been published [24]. A new antithrombogenic membrane with the application of Hydrolink™ NV technology was compared to polysulphone membrane, with the aim of studying the effect of the Hydrolink™ NV dialyzer on platelet count and to evaluate the optimization of anti-coagulation therapy by progressive heparin reduction policy (heparin reduction test). Eleven patients were randomized to dialysis with hydrophilic membrane and 8 patients were dialyzed with a conventional dialyzer. Platelet counts remained within the range of 100,000/mm^3 to 200,000/mm^3 for all patients in both groups. Platelet activation markers PF4 and βTG were measured for the assessment

of platelet adhesion, but no significant changes were found between two groups. More patients in the study group reached heparin-free dialysis without any clotting events than those in the control group. Five out of 10 patients (50%) in the new membrane group reached 0% heparin, whereas 2 out of 8 (25.0%) in the control group reached 0% heparin (p 0.007); 7 out of 10 in the study group and 3 out of 8 in the control group reached ≥60% reduction in heparin dosage (p = 0.007). Further studies showing its wide application, especially in prothrombotic patients, are required.

An intermittent HD combining a heparin-grafted polyacrilonitrile membrane (AN69ST dialyzer) was recently compared with a citrate-enriched dialysate [21]. Study end-points encompassed increased venous pressure (representing increased clotting in the tubing system), variations in urea-reduction ratio (URR) and prematurely ended sessions. Two hundred fifty nine patients participated in the study where 602 sessions were analysed. Clotting events that led to the termination of dialysis were comparable in both groups. In the group with a heparin-grafted membrane, the number of patients with increased venous pressure in the sessions was lower (23 *vs* 70, $p < 0.001$) and UUR was better (0.56 *vs* 0.60, $p < 0.001$) than in the group with citrate-enriched dialysate.

New membranes under investigation, with heparin-like surface modification, seem to be promising in terms of biocompatibility of materials used in hemodialyzers. Due to negatively charged groups, similar to heparin, the modified membranes effectively prolonged the activated partial thromboplastin time (APTT). One approach is to modify polyethersulfone (PES) by providing sulfonic acid ($-SO_3H$) and carboxylic acid groups (-COOH). As a result sulfonated polyethersulfone (SPES) and poly (acrylonitrile-co-acrylic acid-co-vinyl) pyrrolidone) (P(AN-AA-VP)) were created. Both modified membranes showed lowered protein adsorption (bovine serum albumin and fibrinogen) and suppressed platelet adhesion. In comparison with pure PES membrane the modified membranes showed a significant decrease in thrombin-antithrombin generation in experimental studies, as well as less complement activation (lower C3a and C5a levels) [38].

Results of the preclinical study showed that, with the increase of SO_3H to COOH groups ratio, the hydrophilicity, the blood compatibility as well as the cytocompatibility were increased, implying that the SO_3H groups could improve the hemocompatibility of the membranes more effectively than COOH groups. More COOH groups improve antifouling properties. Therefore, the hemocompatibility of the heparin-mimicking membranes could be tuned by controlling the ratios of SO_3H to COOH. It looks like the modified PES composite membranes have a great potential to be used in the field of hemodialysis with heparin-sparing effect [43].

CONCLUSION

There are many different strategies worth taking under consideration while deliberating on the risk of higher hemorrhage or even actively bleeding hemodialyzed patients.

Anticoagulation alternatives to heparin in hemodialysis are used but involve much additional time, effort, close monitoring and yet are not free from some side effects. Other options, such as coated dialyzers or airless tubing, increase cost of procedure and offer at most the reduction of heparin dose. A combination of heparin sparing method is probably more effective than a single one; however, until now hard data to prove this hypothesis does not exist. One must remember that simple principles, for example shorter session (<210 min), lower ultrafiltration, higher blood flow and the avoidance of blood transfusion via dialysis circuit are also crucial in reducing clotting risk.

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